Synthesis of (±)-(4aα,6α,7α,7aα)-hexahydro-6-hydroxy-7-methylcyclopenta[c]pyran-3(1H)-one, a structure common to abelialactone, Aglykon A1, and isoboonein

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lasashi OHBA,* Tsuyoshi HANEISHI, and Tozo FUJII

ıculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan.
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Synthesis of (±)-(4aα,6α,7α,7aα)-hexahydro-6-hydroxy-7-methylcyclopenta[*c*]pyran-3(1*H*)-one [(±)-1] has been achieved through an 8-step route starting from 6,7-dihydrocyclopenta-1,3-dioxin-5(4*H*)-one (4). The identities of synthetic (±)-1 with abelialactone, Aglykon A1, and isoboonein permitted the unequivocal assignment of this common structure and the relative stereochemistry to these cyclopentano-monoterpene lactones.

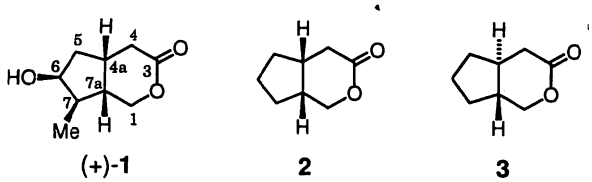
Key words abelialactone; Aglykon A1; isoboonein; cyclopentano-monoterpene lactone; 1,3-dioxin vinylogous ester; carboxyolefination

In 1985, Murai and Tagawa reported the isolation of belialactone, a member of the cyclopentano-monoterpene ıctones,[1] from *Abelia grandiflora* (Caprifoliaceae)[2] and roposed the structure [4a*R*-(4aα,6α,7α,7aα)]-hexahydro--hydroxy-7-methylcyclopenta[*c*]pyran-3(1*H*)-one [(+)-] for it on the basis of an X-ray crystallographic analysis[2] nd its chemical correlation with loganin.[3] Thereafter, ther research groups announced the isolation of two ıctones, named Aglykon A1 (no chiroptical data resented) and isoboonein, from *Cephaelis ipecacuanha* Rubiaceae)[4] and from *Rauwolfia grandiflora* (Apocynaeae),[5] respectively, and independently assigned the same tructure as (+)-**1** to them. These three lactones seem to e identical by comparison of the reported spectral data, ut unambiguous establishment by chemical synthesis is lesirable. In a preparatory study for the synthesis of (±)-**1**, ve presented the stereoselective syntheses of *cis*-hexaıydrocyclopenta[*c*]pyran-3(1*H*)-one (**2**), one of the arent frameworks common to a large number of yclopentano-monoterpene lactones, and its *trans*-isomer **3**) starting from 2-(hydroxymethyl)cyclopentanone by ıdopting the "carboxyolefination/lactonization" technolgy,[6] which was shown later by us to be very effective or the syntheses of several analogous natural lactones.[7] Herein we wish to record the details of the synthesis of (±)-**1** achieved by exploiting this technology.

In designing a synthetic route to (±)-**1**, the 1,3-dioxin vinylogous ester **4**, which had already served successfully as a key intermediate for the syntheses of some natural products,[7,8] seemed most attractive as a starting material because of the diversity of its chemical reactivity.[9] Smith *et al.* have reported that hydroxylation of the enolate, generated *via* treatment of **4** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF), with (+)-(10-camphorsulfonyl)oxaziridine [(+)-**5**] was effected at the α'-position, giving (+)-**6** (14% ee) as a major product in 37% yield.[9] In the present study, however, addition of hexamethylphosphoramide (HMPA) in a similar hydroxylation of **4** with (±)-**5**[10] raised the yield of **6** to 46%. Methylative 1,3-carbonyl transposition of **6** was then achieved with methyl lithium in THF at −78 °C followed by aqueous HCl treatment, affording the cyclopentenone **7** in 92% yield.

It is known that catalytic hydrogenation of the 2,3-disubstituted cyclopentenones containing a hydroxy group at the 4-position (*e.g.*, **7**) provides the cyclopentanone derivatives with the 3,4-*trans*-disposition of substituents due to the addition of hydrogen *syn* to the hydroxy group.[11] Therefore, the two hydroxy groups of **7** were first protected to give the corresponding *tert*-butyldimethylsilyl ether **8** in 93% yield. Hydrogenation of **8** using Adams catalyst and hydrogen in AcOEt occurred predominantly from an orientation opposite to the bulky *tert*-butyldimethylsilyloxy group at the 4-position, giving the 2,3-*cis*-isomer (**9**) and the 2,3-*trans*-isomer (**10**) in 59% and 33% yields, respectively. The structures of **9** and **10** were assigned on the basis of the following NMR spectral and chemical evidence. (i) As shown in formulas **9** and **10** (Chart 1), nuclear Overhauser effect (NOE) experiments revealed *cis* relationships for the vicinal protons at the 3- and 4-positions in both isomers, a *cis* disposition for the two substituents at the 2- and 3-positions of **9**, and a *trans* disposition for the corresponding substituents of **10**. (ii) The C(3)-methyl carbon (δ 9.1) of **9** resonated at higher field than the corresponding carbon (δ 13.8) of **10** due to a steric effect.[12] (iii) On treatment with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in benzene at room temperature for 19 h, the 2,3-*cis*-isomer (**9**) provided the 2,3-*trans*-isomer (**10**) in 84% yield.

For the purpose of effecting carboxyolefination reaction of **10**, a route *via* addition–dehydration seemed to be a favorable choice, based on our previous experiments.[6,7] Thus, addition of the lithium enolate derived from ethyl acetate to **10** was carried out in THF at −78 °C for 2 h, affording the tertiary alcohol **11** in 70% yield as a 57 : 43 mixture of the two possible diastereoisomers. Dehydration of **11** using Martin sulfurane[13] in CH_2Cl_2 proceeded smoothly at room temperature, providing the (*E*)-α,β-unsaturated ester **12a** as a sole product in 93% yield. The



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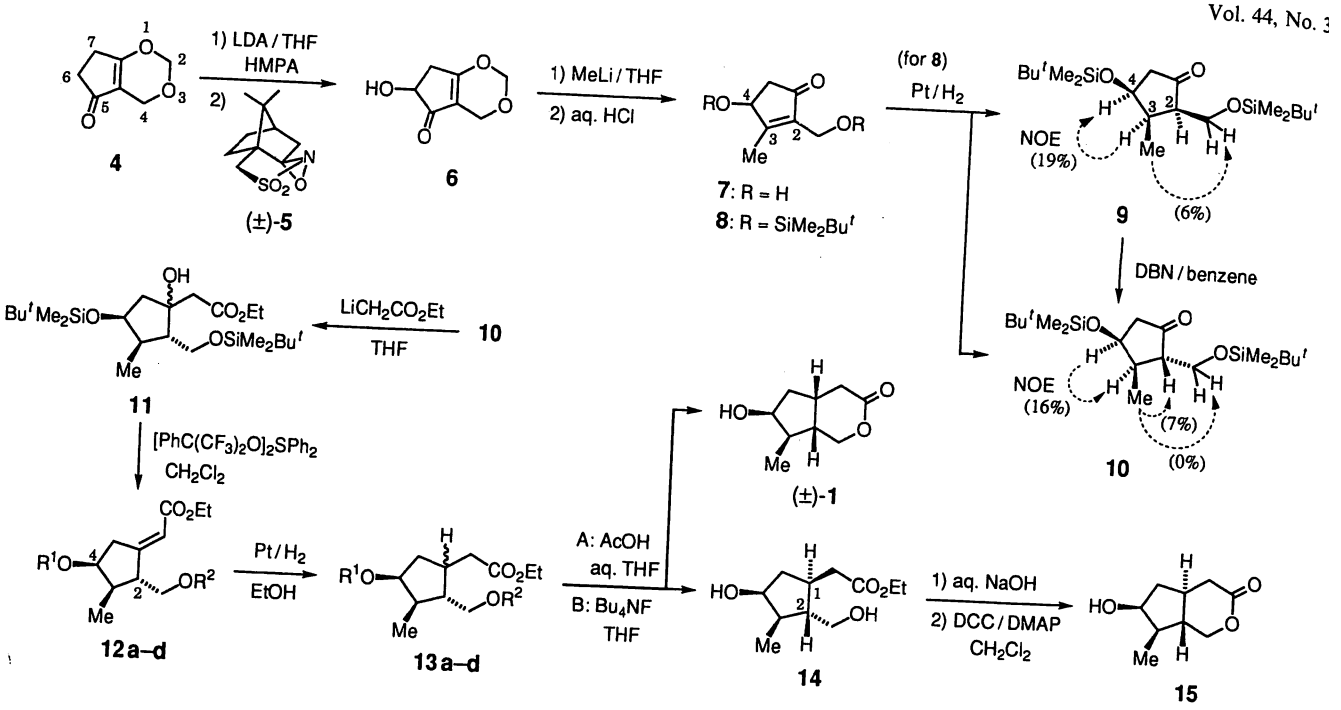
* To whom correspondence should be addressed.



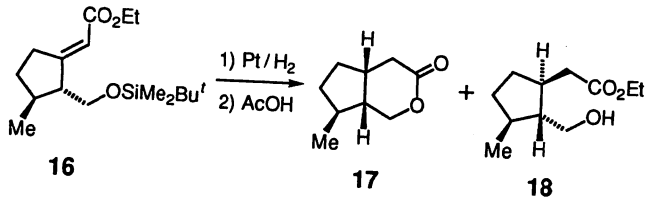
a: $R^1 = R^2 = Bu^tMe_2Si$; **b**: $R^1 = R^2 = H$; **c**: $R^1 = H$, $R^2 = Bu^tMe_2Si$; **d**: $R^1 = H$, $R^2 = Bu^tPh_2Si$

Chart 1

Table 1. Catalytic Hydrogenation of the (*E*)-α,β-Unsaturated Esters **12a—d** and Subsequent Deprotection and/or Cyclization

Compound			Hydrogenation[a]			Deprotection and/or cyclization			
No.	R^1	R^2	Time (h)	Product No.	*cis*:*trans*[d]	Method[c]	Time (h)	Yield[b] (±)-**1**	Yield[b] **14**
12a	Bu^tMe_2Si	Bu^tMe_2Si	6	**13a**	16:84	A	24	14	72
12b	H	H	4	**13b**	18:82	A	20	18	75
12c	H	Bu^tMe_2Si	4	**13c**	67:33	A	24	64	30
12d	H	Bu^tPh_2Si	4	**13d**	69:31	B	24	66	17

a) For details of reaction conditions, see Experimental. *b*) Isolated yield based on **12** after separation by flash chromatography.[19] *c*) Method A: The reaction was performed in AcOH–H_2O–THF (3:1:1, v/v) at room temperature. Method B: The reaction was performed using Bu_4NF in THF at room temperature. *d*) Determined on the basis of ^{1}H-NMR spectral analysis, in which the peak areas for the C(2)-methylene protons of the two isomers were compared.



assignment of geometry in **12a** was based on the fact that an (*E*)-isomer was a major product formed in a similar dehydration[7] and on a comparison of the chemical shift for the C(2)-proton (δ 2.46) in **12a** with those in analogous (*E*)- and (*Z*)-isomers.[6,7]

Catalytic hydrogenation of **12a** over Adams catalyst provided the ester **13a** as a 16:84 diastereoisomeric mixture, which was then subjected to deprotection with AcOH–H_2O–THF (3:1:1, v/v) at room temperature for 24 h. However, a main product obtained in 72% yield (from **12a**) was the 1,2-*trans*-diol **14**, and the yield of the desired (±)-**1** derived from subsequent cyclization was only 14% (from **12a**) (Table 1). Since the structurally analogous *cis*-lactone **17** had been prepared from **16** in 71% yield together with **18** (20% yield) by a similar hydrogenation–deprotective cyclization,[7] the poor yield of (±)-**1** was presumed to be due to steric bulkiness of the *tert*-butyldimethylsilyloxy group at the 4-position of **12a**. Prior to hydrogenation, deprotection of **12a** was therefore performed with AcOH–H_2O–THF (3:1:1, v/v) to furnish the diol **12b** (89% yield), which was then submitted to catalytic hydrogenation and subsequent acid-promoted cyclization. Contrary to our expectation, the 1,2-*trans*-diol **14** was still the main product (75% yield). We next anticipated that introduction of a bulky substituent at the primary hydroxy group of **12b** could depress hydrogenation from the same side as the C(2)-substituent. Toward this end, *tert*-butyldimethylsilyl and *tert*-butyldiphenylsilyl groups were selected and introduced to **12b** to afford **12c** and **12d** in 82% and 94% yields, respectively. As expected, separate catalytic hydrogenations of **12c, d** and subsequent deprotective cyclizations of the resulting esters **13c, d** provided the *cis*-lactone (±)-**1** predominantly in both cases (Table 1). The small coupling constants ($J = 3.5$ and 4.5 Hz) between

C(1)-H's and C(7a)-H measured in the ^{1}H-NMR spectrum of (±)-**1** in $CDCl_3$ indicate that this lactone adopts an iridomyrmecin-type[14] conformation, as previously proposed on the basis of NOE experiments.[15] The 1,2-*trans*-diol **14** was finally subjected to alkaline hydrolysis followed by cyclization with dicyclohexylcarbodiimide (DCC), affording the *trans*-lactone **15** in 80% yield as a labile (to hydrolysis) solid.

The ^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) spectra of the synthetic (±)-**1** were virtually identical with those of natural abelialactone [monohydrate: mp 79.5—80 °C; $[\alpha]_D$ +138.8° (MeOH)][2,16] and Aglykon A1 (mp 93—95 °C).[4,17] The ^{1}H-NMR spectral data for (±)-**1** were also found to match those of natural isoboonein [oil; $[\alpha]_D$ +65.0° (c=0.2, MeOH)] reported in the literature.[5,18] In 1985, Murai *et al.* reported the structural elucidation of abelioside A isolated, along with abelialactone, from *A. grandiflora* and postulated a bis-iridoid structure, in which secologanic acid is esterified with the hydroxy group of (+)-**1**.[2,3] The identical structure was recently proposed for laciniatoside II isolated from *Dipsacus laciniatus* (Dipsacaceae).[15] Again, the ^{1}H-NMR ($CDCl_3$) spectral data for (±)-**1** were in agreement with those of (+)-**1** derived from laciniatoside II.

In conclusion, the above synthesis of (±)-**1** exploiting the "carboxyolefination/lactonization" technology for the 2-(hydroxymethyl)cyclopentanone derivative has established unambiguously the structures and relative stereochemistries of abelialactone, Aglykon A1, and isoboonein as (4aα,6α,7α,7aα)-hexahydro-6-hydroxy-7-methylcyclopenta[*c*]pyran-3(1*H*)-one. It should also be emphasized that the synthetic potential of the 1,3-dioxin vinylogous ester **4**, exemplified previously by the syntheses of several cyclopentano-monoterpene lactones,[7] has now been extended to cover the synthesis of the more highly substituted analogue (±)-**1**.

Experimental

General Notes All melting points were determined by using a Büchi model 530 capillary melting point apparatus and are corrected. TLC was run on Merck precoated silica gel 60 F_{254} plates (0.25-mm thickness). Flash chromatography[19] was carried out by using Merck silica gel 60 (No. 9385). Spectra reported herein were recorded on a Hitachi M-80 mass spectrometer, either a JASCO A-202 or a Shimadzu FTIR-8100 IR spectrophotometer, or either a JEOL JNM-EX-270 (^{13}C 67.8 MHz) or a JEOL JNM-GSX-500 (^{1}H 500 MHz, ^{13}C 125.65 MHz) NMR instrument. Chemical shifts are reported in ppm downfield from internal Me_4Si. Elemental analyses and MS measurements were performed by Mr. Itatani and his associates at Kanazawa University. The following abbreviations are used: br=broad, d=doublet, dd=doublet-of-doublets, ddd=doublet-of-dd's, dddd=doublet-of-ddd's, ddddd=doublet-of-dddd's, ddq=doublet-of-doublets-of-quartets, dq=doublet-of-quartets, m=multiplet, q=quartet, s=singlet, t=triplet.

(±)-(10-Camphorsulfonyl)oxaziridine [(±)-5][10] This compound was prepared from (±)-10-camphorsulfonic acid in a manner similar to that described in the literature for (+)-**5**.[20] Recrystallization from 2-propanol afforded an analytical sample as colorless prisms, mp *156—157 °C*; *MS m/z*: 229 (M^+). *Anal.* Calcd for $C_{10}H_{15}NO_3S$: C, 52.38; H, 6.59; N, 6.11. Found: C, 52.20; H, 6.78; N, 5.97. The ^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) spectra of this sample were virtually identical with those of (+)-**5** reported in the literature.[20]

(±)-6,7-Dihydro-6-hydroxycyclopenta-1,3-dioxin-5(4*H*)-one (6) A stirred solution of diisopropylamine (3.7 ml, 26.4 mmol) in dry THF (100 ml) was cooled to 0 °C in an atmosphere of Ar, and a 1.60 M solution (16.5 ml, 26.4 mmol) of *n*-BuLi in hexane was added dropwise. After 20 min, the mixture was cooled to −78 °C, and a solution of the 1,3-dioxin vinylogous ester **4**[9] (3.08 g, 22.0 mmol) in dry THF (45 ml) containing HMPA (4.6 ml, 26.4 mmol) was added dropwise over 20 min. After 1 h, a solution of (±)-**5** (10.1 g, 44.0 mmol) in dry THF (80 ml) was added dropwise over 20 min, and the mixture was further stirred at −78 °C for 30 min and at 0 °C for 30 min. The reaction was quenched by adding saturated aqueous NH_4Cl (30 ml), and the mixture was warmed to room temperature. The aqueous layer was separated from the organic layer and extracted with CH_2Cl_2. The CH_2Cl_2 extracts and the above organic layer were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave a yellow solid, which was then subjected to flash chromatography[19] [AcOEt–hexane (2:1, v/v)]. Earlier fractions afforded the starting vinylogous ester **4** (920 mg, 30% recovery).

Later fractions of the above chromatography gave a yellow solid (2.09 g), which was recrystallized from AcOEt–hexane (1:1, v/v) to provide a first crop (0.95 g) of **6** as slightly yellow needles, mp 95—96 °C. The IR ($CHCl_3$) and ^{1}H-NMR ($CDCl_3$) data for this sample were virtually identical with those of authentic **6** (mp 99.5—100.5 °C) reported in the literature.[9] A second crop (0.63 g) was obtained by concentration of the mother liquor from the above recrystallization under reduced pressure and subsequent purification of the residue by flash chromatography[19] [CH_2Cl_2–EtOH (20:1, v/v)]. The total yield of **6** was 1.58 g (46%).

(±)-4-Hydroxy-2-(hydroxymethyl)-3-methyl-2-cyclopenten-1-one (7) A solution of **6** (1.23 g, 7.9 mmol) in dry THF (60 ml) was cooled to −78 °C in an atmosphere of Ar, and a 1.4 M solution (28 ml, 39.2 mmol) of MeLi in ether was added dropwise over 20 min. After the mixture had been stirred for a further 2 h, 10% aqueous HCl (35 ml) was added. The reaction mixture was then allowed to warm to room temperature and stirred for 30 min. The aqueous layer, after having been neutralized with anhydrous K_2CO_3, was separated from the organic layer and concentrated *in vacuo*. The residual yellow solid was continuously extracted with AcOEt for 3 h using a Soxhlet extractor. The AcOEt extracts and the above organic layer were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave a yellow oil. Purification of the oil by flash chromatography[19] [CH_2Cl_2–EtOH (10:1, v/v)] yielded **7** (1.03 g, 92%) as a colorless oil, MS *m/z*: 142 (M^+); IR ν_{max}^{film} cm^{-1}: 3380 (OH), 1690 (CO), 1645 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 2.16 (3H, s, Me), 2.2 (2H, br, two OH's), 2.32 (1H, d, J=18.5 Hz) and 2.82 (1H, dd, J=18.5, 6 Hz) [C(5)-H's], 4.34 (2H, s, CH_2OH), 4.74 [1H, d, J=6 Hz, C(4)-H].

(±)-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3-methyl-2-cyclopenten-1-one (8) A mixture of **7** (1.03 g, 7.25 mmol), imidazole (3.81 g, 56.0 mmol), and *N*,*N*-dimethylformamide (DMF) (10 ml) was stirred under ice-cooling, and a solution of *tert*-butylchlorodimethylsilane (4.22 g, 28.0 mmol) in DMF (8 ml) was added. After having been stirred at room temperature for 1 h, the mixture was poured into cold H_2O (50 ml) and extracted with ether (3 × 50 ml). The ethereal extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave a slightly yellow oil. Purification of the oil by flash chromatography[19] [hexane–AcOEt (15:1, v/v)] afforded **8** (2.51 g, 93%) as a colorless oil, MS *m/z*: 370 (M^+); IR ν_{max}^{film} cm^{-1}: 1713 (CO), 1661 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 0.07, 0.08, 0.11, and 0.14 (12H, s each, two $SiMe_2$'s), 0.89 and 0.92 (18H, s each, two *tert*-Bu's), 2.16 [3H, s, C(3)-Me], 2.24 (1H, dd, J=18, 2.5 Hz) and 2.70 (1H, dd, J=18, 6 Hz) [C(5)-H's], 4.34 and 4.39 [2H, AB type d's, J=13 Hz, C(2)-CH_2O], 4.65 [1H, br d, J=6 Hz, C(4)-H].

(±)-(2α,3α,4α)-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3-methylcyclopentanone (9) and (±)-(2α,3β,4β)-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3-methylcyclopentanone (10) A solution of **8** (593 mg, 1.6 mmol) in AcOEt (20 ml) was hydrogenated over Adams catalyst (30 mg) at atmospheric pressure and room temperature for 3 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to leave a colorless oil, which was subjected to flash chromatography[19] [hexane–CH_2Cl_2 (1:1, v/v)]. Earlier fractions provided **10** (194 mg, 33%) as a colorless solid, mp 47.5—48.5 °C. Recrystallization of the solid from hexane gave an analytical sample as colorless prisms, mp 49.5—50 °C; MS *m/z*: 315 (M^+ − *tert*-Bu); IR ν_{max}^{Nujol} 1754 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ: 0.01, 0.03, 0.04, and 0.07 (12H, s each, two $SiMe_2$'s), 0.84 and 0.86 (18H, s each, two *tert*-Bu's), 1.11 [3H, d, J=7 Hz, C(3)-Me], 1.98 [1H, ddd, J=11, 3.5, 3 Hz, C(2)-H], 2.23 (1H, dd, J=17.5, 4 Hz) and 2.27 (1H, d, J=17.5 Hz) [C(5)-H's], 2.37 [1H, ddq, J=11, 3.5, 7 Hz, C(3)-H], 3.64

(1H, dd, J=10.5, 3 Hz) and 4.02 (1H, dd, J=10.5, 3.5 Hz) [C(2)-CH_2O], 4.32 [1H, dd, J=4, 3.5 Hz, C(4)-H]; ^{13}C-NMR ($CDCl_3$) δ: −4.9, −4.9, −4.7, and −4.7 (two $SiMe_2$'s), 13.8 [C(3)-Me], 18.1 and 18.2 (two CMe_3's), 25.8 (two CMe_3's), 38.5 [C(3)], 49.8 [C(5)], 54.2 [C(2)], 59.5 [C(2)-CH_2O], 71.6 [C(4)], 218.0 (CO). *Anal.* Calcd for $C_{19}H_{40}O_3Si_2$: C, 61.23; H, 10.82. Found: C, 61.19; H, 10.70.

Later fractions of the above chromatography afforded **9** (352 mg, 59%) as a colorless oil, MS m/z: 315 ($M^+ - tert$-Bu); IR ν_{max}^{film} 1746 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ: 0.046, 0.050, 0.06, and 0.09 (12H, s each, two $SiMe_2$'s), 0.89 and 0.90 (18H, s each, two *tert*-Bu's), 1.01 [3H, d, J=7 Hz, C(3)-Me], 2.20 (1H, dd, J=18.5, 6.5 Hz) and 2.43 (1H, dd, J=18.5, 6.5 Hz) [C(5)-H's], 2.48—2.58 [2H, m, C(2)-H and C(3)-H], 3.74 (1H, dd, J=10, 9 Hz) and 3.94 (1H, dd, J=10, 4.5 Hz) [C(2)-CH_2O], 4.36 [1H, ddd, J=6.5, 6.5, 5 Hz, C(4)-H]; ^{13}C-NMR ($CDCl_3$) δ: −4.9, −4.9, −4.8, and −4.8 (two $SiMe_2$'s), 9.1 [C(3)-Me], 18.1 and 18.2 (two CMe_3's), 25.8 and 25.9 (two CMe_3's), 38.8 [C(3)], 46.1 [C(5)], 55.7 [C(2)], 60.0 [C(2)-CH_2O], 71.2 [C(4)], 216.0 (CO).

Isomerization of 9 to 10 A mixture of **9** (56 mg, 0.15 mmol), DBN (4 mg, 0.03 mmol), and benzene (2.5 ml) was stirred at room temperature for 19 h. The reaction mixture was then washed successively with 5% aqueous HCl and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification of the residual oil by flash chromatography[19] [hexane–CH_2Cl_2 (1:1, v/v)] provided **10** (47 mg, 84%) as a colorless solid, mp 47.5—48.5 °C, which was identical (by comparison of the IR and ^{1}H-NMR spectra and TLC behavior) with the one obtained directly from **8** by hydrogenation (*vide supra*).

(±)-(2α,3β,4β)-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-1-hydroxy-3-methylcyclopentaneacetic Acid Ethyl Ester (11) A stirred solution of diisopropylamine (0.21 ml, 1.5 mmol) in dry THF (5 ml) was cooled to −78 °C in an atmosphere of Ar, and a 1.50 M solution (1.0 ml, 1.5 mmol) of *n*-BuLi in hexane was added dropwise. After the mixture had been stirred for 30 min, AcOEt (0.14 ml, 1.4 mmol) was added, and stirring was continued for 20 min. A solution of **10** (418 mg, 1.12 mmol) in dry THF (2 ml) was then added dropwise over 5 min, and the mixture was stirred at −78 °C for a further 2 h. The reaction was quenched by adding saturated aqueous NH_4Cl (2 ml), and the mixture was allowed to warm to room temperature. The aqueous layer was separated from the organic layer and extracted with ether (3 × 10 ml). The ethereal extracts and the above organic layer were combined, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification of the residual oil by flash chromatography[19] [hexane–AcOEt (15:1, v/v)] furnished **11** (362 mg, 70%) as a colorless oil, MS m/z: 415 ($M^+ - OEt$), 403 ($M^+ - tert$-Bu); IR ν_{max}^{film} cm^{-1}: 3520 (OH), 1736 and 1719 (diastereoisomeric ester CO's); ^{1}H-NMR ($CDCl_3$) major isomer δ: 0.030, 0.034, 0.07, and 0.08 (s each, two $SiMe_2$'s), 0.87 and 0.89 (s each, two *tert*-Bu's), 1.03 [d, J=7 Hz, C(3)-Me], 1.26 (t, J=7 Hz, OCH_2Me), 1.89 (dd, J=13.5, 4 Hz) and 2.00 (d, J=13.5 Hz) [C(5)-H's], 1.9—2.05 [m, C(2)-H and C(3)-H], 2.60 and 2.75 (d each, J=14.5 Hz, CH_2CO_2Et), 3.55 (dd, J=10.5, 4.5 Hz) and 3.83 (dd, J=10.5, 3.5 Hz) [C(2)-CH_2O], 3.95 (s, OH), 4.1—4.2 [m, OCH_2Me and C(4)-H]; minor isomer δ: 0.03, 0.04, 0.07, and 0.08 (s each, two $SiMe_2$'s), 0.88 and 0.90 (s each, two *tert*-Bu's), 0.94 [d, J=7 Hz, C(3)-Me], 1.26 (t, J=7 Hz, OCH_2Me), 1.71 [ddd, J=11, 6, 4 Hz, C(2)-H], 1.9—2.05 [m, C(3)-H], 1.97 (dd, J=14, 5 Hz) and 2.07 (dd, J=14, 2.5 Hz) [C(5)-H's], 2.57 and 2.86 (d each, J=14.5 Hz, CH_2CO_2Et), 3.80 (dd, J=10.5, 6 Hz) and 3.90 (dd, J=10.5, 4 Hz) [C(2)-CH_2O], 4.1—4.2 [m, OCH_2Me, C(4)-H and OH]. The ^{1}H-NMR spectrum indicated that the oil was a 57:43 mixture of the two possible diastereoisomers.

(±)-(2α,3β,4β)-(*E*)-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3-methylcyclopentylidene]acetic Acid Ethyl Ester (12a) A mixture of **11** (437 mg, 0.95 mmol), bis[2,2,2-trifluoro-1-phenyl-1-(trifluoromethyl)ethoxy] diphenyl sulfurane[13] (770 mg, 1.14 mmol), and dry CH_2Cl_2 (18 ml) was stirred in an atmosphere of N_2 at room temperature for 3 h. The reaction mixture was then poured into H_2O (10 ml) and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification of the residual oil by flash chromatography[19] [hexane–AcOEt (20:1, v/v)] gave **12a** (390 mg, 93%) as a colorless oil, MS m/z: 442 (M^+); IR ν_{max}^{film} cm^{-1}: 1717 (ester CO), 1655 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 0.03, 0.036, 0.039, and 0.042 (12H, s each, two $SiMe_2$'s), 0.86 and 0.87 (18H, s each, two *tert*-Bu's), 1.02 [3H, d, J=6.5 Hz, C(3)-Me], 1.27 (3H, t, J=7 Hz, OCH_2Me), 1.88 [1H, m, C(3)-H], 2.46 [1H, m, C(2)-H], 2.69 (1H, dddd, J=19, 5, 3, 2.5 Hz) and 3.08 (1H, ddd, J=19, 2, 1.5 Hz) [C(5)-H's], 3.67 and 3.74 [1H each, dd, J=10, 5 Hz, C(2)-CH_2O], 4.14 and 4.16 (2H, dq each, J=10.5, 7 Hz, OCH_2Me), 4.19 [1H, m, C(4)-H], 5.88 (1H, ddd, J=2.5, 2.5, 2 Hz, $CHCO_2Et$).

(±)-(2α,3β,4β)-(*E*)-[4-Hydroxy-2-(hydroxymethyl)-3-methylcyclopentylidene]acetic Acid Ethyl Ester (12b) A solution of **12a** (297 mg, 0.67 mmol) in AcOH–H_2O–THF (3:1:1, v/v) (15 ml) was stirred at room temperature for 46 h. The reaction mixture was then concentrated *in vacuo* to leave a colorless oil, which was co-evaporated *in vacuo* with two 5-ml portions of benzene. Purification of the residual oil by flash chromatography[19] [AcOEt–hexane (1:1, v/v)] yielded **12b** (128 mg, 89%) as a colorless oil, MS m/z: 214 (M^+); IR ν_{max}^{film} cm^{-1}: 3400 (OH), 1696 (ester CO), 1655 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 1.13 [3H, d, J=7 Hz, C(3)-Me], 1.28 (3H, t, J=7 Hz, OCH_2Me), 1.75 (2H, br, two OH's), 2.01 [1H, m, C(3)-H], 2.53 [1H, m, C(2)-H], 2.81 (1H, dddd, J=19, 5, 3, 2.5 Hz) and 3.18 (1H, ddd, J=19, 2, 1.5 Hz) [C(5)-H's], 3.73 (1H, dd, J=11.5, 4.5 Hz) and 3.93 (1H, dd, J=11.5, 4 Hz) (CH_2OH), 4.16 (2H, q, J=7 Hz, OCH_2Me), 4.27 [1H, dd, J=5, 4 Hz, C(4)-H], 5.93 (1H, ddd, J=2.5, 2.5, 2 Hz, $CHCO_2Et$).

(±)-(2α,3β,4β)-(*E*)-[2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-methyl]-4-hydroxy-3-methylcyclopentylidene]acetic Acid Ethyl Ester (12c) A mixture of **12b** (107 mg, 0.50 mmol), imidazole (75 mg, 1.10 mmol), *tert*-butylchlorodimethylsilane (83 mg, 0.55 mmol), and DMF (1 ml) was stirred at 0 °C in an atmosphere of N_2 for 1.5 h. The reaction mixture was then poured into H_2O (4 ml) and extracted with ether (3 × 10 ml). The ethereal extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave a colorless oil. Purification of the oil by flash chromatography[19] [hexane–AcOEt (3:1, v/v)] gave **12c** (135 mg, 82%) as a colorless oil, CIMS m/z: 329 (MH^+); IR ν_{max}^{film} cm^{-1}: 3450 (OH), 1713 (ester CO), 1655 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 0.03 and 0.04 (6H, s each, $SiMe_2$), 0.87 (9H, s, *tert*-Bu), 1.12 [3H, d, J=7.5 Hz, C(3)-Me], 1.27 (3H, t, J=7 Hz, OCH_2Me), 1.34 (1H, d, J=3.5 Hz, OH), 1.96 [1H, m, C(3)-H], 2.48 [1H, m, C(2)-H], 2.76 (1H, dddd, J=19, 5, 3.5, 2.5 Hz) and 3.19 (1H, ddd, J=19, 2, 1.5 Hz) [C(5)-H's], 3.71 and 3.76 [1H each, dd, J=10.5, 5 Hz, C(2)-CH_2O], 4.15 (2H, q, J=7 Hz, OCH_2Me), 4.25 [1H, ddd, J=3.5 Hz each, C(4)-H], 5.91 (1H, ddd, J=2.5, 2.5, 2 Hz, $CHCO_2Et$).

(±)-(2α,3β,4β)-(*E*)-[2-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-methyl]-4-hydroxy-3-methylcyclopentylidene]acetic Acid Ethyl Ester (12d) A mixture of **12b** (21.2 mg, 0.10 mmol), imidazole (21 mg, 0.30 mmol), and DMF (0.2 ml) was stirred in an atmosphere of N_2 under ice-cooling, and a solution of *tert*-butylchlorodiphenylsilane (42 mg, 0.15 mmol) in DMF (0.2 ml) was added. After having been stirred at room temperature for 1.5 h, the reaction mixture was worked up as described above for **12c**, giving **12d** (42.1 mg, 94%) as a colorless oil, CIMS m/z: 453 (MH^+); IR ν_{max}^{film} cm^{-1}: 3450 (OH), 1713 (ester CO), 1655 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 1.03 (9H, s, *tert*-Bu), 1.05 [3H, d, J=7 Hz, C(3)-Me], 1.29 (3H, t, J=7 Hz, OCH_2Me), 1.33 (1H, br, OH), 2.06 [1H, m, C(3)-H], 2.51 [1H, m, C(2)-H], 2.81 (1H, dddd, J=19, 5, 3.5, 2.5 Hz) and 3.21 (1H, br d, J=19 Hz) [C(5)-H's], 3.75 and 3.80 [1H each, dd, J=10.5, 4.5 Hz, C(2)-CH_2O], 4.16 and 4.17 (2H, dq each, J=10.5, 7 Hz, OCH_2Me), 4.26 [1H, br, C(4)-H], 5.89 (1H, ddd, J=2.5, 2.5, 2 Hz, $CHCO_2Et$), 7.25—7.45 (6H) and 7.6—7.65 (4H) (m each, two Ph's).

(±)-(4aα,6α,7α,7aα)-Hexahydro-6-hydroxy-7-methylcyclopenta[*c*]-pyran-3(1*H*)-one [(±)-Abelialactone, Racemic Aglykon A1, (±)-Isoboonein] [(±)-1] and (±)-(1α,2β,3α,4α)-4-Hydroxy-2-(hydroxymethyl)-3-methylcyclopentaneacetic Acid Ethyl Ester (14) A Typical Example: A solution of **12c** (102 mg, 0.31 mmol) in EtOH (7 ml) was hydrogenated over Adams catalyst (15 mg) at atmospheric pressure and room temperature for 4 h. Removal of the catalyst by filtration and concentration of the filtrate *in vacuo* provided (±)-(2α,3β,4β)-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-4-hydroxy-3-methylcyclopentaneacetic acid ethyl ester (**13c**) (101 mg) as a colorless oil, which was found to be a 67:33 mixture of the two possible diastereoisomers on the basis of ^{1}H-NMR spectral analysis. This oil, after addition of AcOH–H_2O–THF (3:1:1, v/v) (6 ml), was stirred at room temperature for 24 h, and the reaction mixture was concentrated *in vacuo*. The residual oil was co-evaporated *in vacuo* with two 3-ml portions of benzene to leave a colorless oil, which was then subjected to flash chromatography[19] [AcOEt–hexane (2:1, v/v)]. Earlier fractions gave **14** (20.1 mg, 30% from **12c**) as a colorless oil, MS m/z: 216 (M^+); IR ν_{max}^{film} cm^{-1}: 3400 (OH), 1713 (ester CO); ^{1}H-NMR ($CDCl_3$) δ: 1.05 [3H, d, J=7 Hz, C(3)-Me], 1.26 (3H, t, J=7 Hz, OCH_2Me), 1.48 (1H, ddd, J=13.5, 5,

2 Hz) and 2.18 (1H, ddd, J=13.5, 10, 5 Hz) [C(5)-H's], 1.59 [1H, m, C(2)-H], 1.71 [1H, m, C(3)-H], 1.78 (br, two OH's), 2.26 [1H, m, C(1)-H], 2.49 (1H, dd, J=16.5, 6 Hz) and 2.65 (1H, dd, J=16.5, 7.5 Hz) (CH_2CO_2Et), 3.57 (1H, dd, J=11, 6 Hz) and 3.71 (1H, dd, J=11, 3.5 Hz) (CH_2OH), 4.09 [1H, ddd, J=5, 5, 2 Hz, C(4)-H], 4.14 (2H, q, J=7 Hz, OCH_2Me).

Later fractions of the above chromatography furnished (±)-**1** (34.0 mg, 64% from **12c**) as a colorless solid. Recrystallization of the solid from hexane–AcOEt (2:1, v/v) afforded an analytical sample as colorless needles, mp 99—101 °C; MS *m/z* (relative intensity): 170 (M^+, 7), 152 (12), 139 (100), 126 (44), 124 (43), 111 (47), 110 (31), 97 (35), 83 (36), 81 (41), 69 (35), 55 (31), 43 (40); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620 (OH), 1740 (CO); ^{1}H-NMR ($CDCl_3$) δ: 1.08 [3H, d, J=7 Hz, C(7)-Me], 1.41 (1H, ddd, J=14, 10.5, 3.5 Hz) and 2.06 (1H, dd, J=14, 8 Hz) [C(5)-H's], 1.68 (1H, br, OH), 1.92 [1H, ddq, J=10.5, 3.5, 7 Hz, C(7)-H], 2.16 [1H, dddd, J=10.5, 10.5, 4.5, 3.5 Hz, C(7a)-H], 2.38 (1H, dd, J=15, 4 Hz) and 2.64 (1H, dd, J=15, 7 Hz) [C(4)-H's], 2.94 [1H, ddddd, J=10.5, 10.5, 8, 7, 4 Hz, C(4a)-H], 4.13 [1H, dd, J=3.5 Hz each, C(6)-H], 4.15 (1H, dd, J=11.5, 3.5 Hz) and 4.32 (1H, dd, J=11.5, 4.5 Hz) [C(1)-H's]; ^{13}C-NMR ($CDCl_3$) δ: 12.7 [C(7)-Me], 32.7 [C(4a)], 34.5 [C(4)], 41.5 [C(7)], 41.6 [C(5)], 41.7 [C(7a)], 68.6 [C(1)], 75.6 [C(6)], 173.4 [C(3)]; high-resolution MS Calcd for $C_9H_{14}O_3$: 170.0943, Found: 170.0965. *Anal.* Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.36; H, 8.34. The ^{1}H-NMR and ^{13}C-NMR spectra of this sample were virtually identical with those of natural abelialactone[2,16] and Aglykon A1.[4,17] These spectral data were also in general agreement with those of natural isoboonein described in the literature.[5,18]

Catalytic hydrogenation of **12a, b, d** and subsequent deprotection and/or acid-catalyzed cyclization of the resulting **13a, b** were separately effected in a manner similar to that described above. The results are given in Table 1. On the other hand, deprotection of **13d** was carried out as follows. A solution of **13d**, obtained from **12d** (36.0 mg, 0.08 mmol), in THF (1 ml) was stirred in an atmosphere of Ar under ice-cooling, and a 1.0 M solution (0.35 ml, 0.35 mmol) of tetrabutylammonium fluoride in THF was added. After having been stirred at room temperature for 24 h, the reaction mixture was concentrated *in vacuo* to leave a colorless oil. Flash chromatography[19] of this oil was conducted as described above, giving **14** (2.9 mg, 17% from **12d**) as a colorless oil and (±)-**1** (8.9 mg, 66% from **12d**) as a colorless solid, which were identical (by comparison of ^{1}H-NMR spectra and TLC behavior) with authentic **14** and (±)-**1** prepared from **12c** (*vide supra*).

(±)-(4aα,6β,7β,7aβ)-Hexahydro-6-hydroxy-7-methylcyclopenta[*c*]-pyran-3(1*H*)-one (15) A solution of **14** (65 mg, 0.30 mmol) in EtOH (1 ml) was stirred under ice-cooling, and 1 N aqueous NaOH (1 ml) was added. The mixture was then stirred at room temperature for 30 min, concentrated *in vacuo*, and acidified with 6 N aqueous HCl. After addition of acetone–CH_2Cl_2 (1:1, v/v) (30 ml), the organic solution was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residual colorless oil was dissolved in dry CH_2Cl_2 (20 ml), and DCC (75 mg, 0.36 mmol) and 4-dimethylaminopyridine (DMAP) (5 mg) were added. The mixture was then stirred at room temperature for 1 h and concentrated *in vacuo* to leave a colorless solid. Purification of the solid by flash chromatography[19] [CH_2Cl_2–EtOH (20:1, v/v)] furnished **15** (41 mg, 80%) as a colorless solid. Recrystallization from hexane–AcOEt (2:1, v/v) afforded an analytical sample as colorless needles, mp 76.5—78 °C; MS *m/z* (relative intensity): 170 (M^+, 12), 152 (20), 126 (72), 111 (66), 93 (51), 83 (94), 82 (60), 81 (93), 69 (72), 68 (58), 67 (85), 55 (89), 43 (75), 41 (100); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620 (OH), 1725 (CO); ^{1}H-NMR ($CDCl_3$) δ: 1.06 [3H, d, J=7 Hz, C(7)-Me], 1.25 (1H, ddd, J=14, 10.5, 3.5 Hz) and 2.52 (1H, ddd, J=14, 7, 7 Hz) [C(5)-H's], 1.54 (1H, br, OH), 1.62 [1H, ddq, J=11, 7, 7 Hz, C(7)-H], 1.73 [1H, dddd, J=11, 11, 11, 5 Hz, C(7a)-H], 1.77 [1H, m, C(4a)-H], 2.34 (1H, dd, J=17.5, 12.5 Hz) and 2.89 (1H, dd, J=17.5, 5 Hz) [C(4)-H's], 4.05 (1H, dd, J=11, 10.5 Hz) and 4.57 (1H, dd, J=10.5, 5 Hz) [C(1)-H's], 4.33 [1H, ddd, J=7, 7, 3.5 Hz, C(6)-H]; ^{13}C-NMR ($CDCl_3$) δ: 11.6 [C(7)-Me], 38.0 [C(4)], 38.8 [C(4a)], 40.8 [C(5)], 41.9 [C(7)], 44.7 [C(7a)], 74.1 [C(1)], 74.4 [C(6)], 170.3 [C(3)]; high-resolution MS Calcd for $C_9H_{14}O_3$: 170.0943, Found: 170.0954. *Anal.* Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.38; H, 8.36. This sample was found to revert slowly to the hydroxy carboxylic acid on standing at room temperature.

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